REMARKS

To achieve an expeditious allowance, applicants maintained only claim 15 from the rejected claims and amended the same to render moot the rejections under section 112, all without prejudice or disclaimer.

The only rejection remaining is the section 103 rejection of claim 15 over Knox in view of Dupuis.

Under controlling law, this rejection cannot be maintained.

The decisions of the Federal Circuit in *Takeda Chemical Industries Ltd. v. Alphapharm Pty. Ltd.*, 83 USPQ2d 1169 (Fed. Cir. 2007), and *Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd. et al.*, 87 USPQ2d 1452 (Fed. Cir. 2008) are highly relevant to the allegations. Both of these controlling decisions post date *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 82 USPQ2d 1385 (2007) and specifically discuss the requirements of establishing obviousness, especially in the chemical arts regarding structural obviousness.

One of the issues in *Takeda* was whether picking a specific compound as a starting point (lead compound) from the prior art disclosing it and several others is obvious without a reason leading to its choice. The Federal Circuit's answer was no.

The prior art reference in *Takeda* taught the exact same use for the compounds as claimed in the later application (antidiabetic treatment), taught 34 compounds specifically from a broad generically disclosed formula, including the specific compound of interest in the later application, the prosecution history of the prior art reference supplied test data for nine specific compounds, including the specific compound of interest, the compound of interest was specifically claimed in one of the patents in the prior art patent family, i.e., a claim specifically was directed to the compound of interest alone (see claim 4 of US 4,444,779), and the prosecution history thereof included a statement to the effect that the claimed compounds became important, especially the compound of interest.

A separate prior art document tested 101 various prior art compounds, including the compound of interest, and indicated some side effects associated with the compound of interest.

The lower court held, which holding was upheld by the Federal Circuit, that the selection of the compound of interest as a lead compound was not obvious in view of the prior art. The lower court held that any "suggestion to select" the compound of interest was negated by the separate prior art document testing various prior art compounds. (Emphasis added.) The Federal Circuit rejected arguments relying on *KSR* that "the claimed compounds

would have been obvious because the prior art compound fell within 'the objective reach of the claims.'"

Thus, it is clear that the law requires "suggestion to select" the compounds of interest from the prior art, and it is not adequate that a compound merely fall within the objective reach of a claim.

The Federal Circuit in *Eisai* characterized the holding of Takeda by stating that "obviousness based on structural similarity thus can be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (i.e., a lead compound) in a particular way to achieve the claimed compound." Emphasis added.

The court went on to summarize the state of the law of obviousness, especially as it pertains to chemical arts, as follows:

> First, KSR assumes a starting reference point or points in the art, prior to the time of invention, from which a skilled artisan might **identify a problem and pursue potential solutions**. Second, KSR presupposes that the record up to the time of invention would **give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound**. See Takeda, 492, F.3d at 1357 ("Thus, ***in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness*** of a new claimed compound."). Third, the Supreme Court's analysis in KSR presumes that the record before the time of invention would **supply some reasons for narrowing the prior art universe to a "finite number of identified, predictable solutions**," 127 S. Ct. at 1742. In Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc., 520 F.3d 1358, 1364 (Fed. Cir. 2008), this court further explained that **this "easily traversed, small and finite number of alternatives . . . might support an inference of obviousness." To the extent an art is unpredictable, as the chemical arts often are, KSR's focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable**. (Emphasis added.)

The compound of the claims in *Eisai*, i.e., Lansoprazole, was in an art where the core of the compound was known and described in a class of compounds by a reference, i.e., Brändström. Rabeprazole, a specific prior art compound, had the same core and substituents

thereon with the exception of an $OCH_2CH_2CH_2OCH_3$ group in the 4-position, where the claimed Lansoprazole has an OCH_2CF_3 group. Omeprazole, another compound sharing the same core has an OCH_3 group in the 4-position. The Federal Circuit even taking the evidence most favorable to the movant on Summary Judgment challenging the validity of the patent did not find obviousness. There was evidence in the record that the fluorinated substituent on the lead, i.e., Lansoprazole, which was selected as the allegedly obvious lead by the movant, provided a special path to achieving lipophilicity. Without discernible reason on the record why one of ordinary skill in the art would have modified this group, which was known to provide lipophilicity, the Federal Circuit held that there was no obviousness.

In the present case the Office Action points to compounds 1506-00404 and 1506-08722 of Knox. No reason whatsoever is provided for the selection of these compounds from the numerous compounds of Knox. Thus, even at this early stage of the rejection, the Office Action has not carried its burden as required by the holdings of the recent cases on structural obviousness discussed above.

Additionally, nothing in the Office Action even establishes that these compounds should be modified in any way to achieve a biphenyl compound (see the compounds of claim 15). Neither compound 1506-00404 nor 1506-08722 are compounds that even remotely resemble a compound of the present claims. Neither one contains, e.g., a biphenyl moiety. Moreover, not a single compound present in Knox, over reasonable review of this reference, appears to contain a biphenyl moiety, and also no such allegation is made herein. Instead, merely the generic broad allegation is made that "the general teaching guided by the particular exemplification provided guidance in picking and choosing among the various Markush elements." And thereafter no specific allegation is made regarding how or why and which compound of Knox would be modified, again by which the Office Action fails to carry its burden in establishing the alleged obviousness.

Moreover, even the generic allegation is improper under controlling precedent. It is long standing well-settled law that it is not proper to combine the generic disclosure with the individual species, or parts of various specific species with parts of other species in order to establish obviousness. One of ordinary skill in the art is not provided with any guidance by the generic formula as to how and which substituent(s) should be modified on any single specific compound or how parts of one compound should be used to replace parts of another compound. See *In re Jones*, 958 F.2d 347, 21 U.S.P.Q. 2d 1941 (Fed. Cir. 1992) and *In re Baird*, 16 F.2d 380, 29 U.S.P.Q. 2d 1550 (Fed. Cir. 1994).

Note in this regard, particularly, the analysis used by the Court in *Jones*. The group at issue in Jones had the structure $-NH_2-CH_2CH_2-O-CH_2CH_2OH$. The PTO tried to rely on the single reference's compound having two CH_2CH_2OH groups attached to a single N atom, instead of linked together as shown above. The Court stated that one could not ignore the fact that the two CH_2CH_2OH groups were not joined together to form the ether linkage-containing group required in the claim. One could not simply rely on the "$-CH_2CH_2O-$" features of the reference; one had to consider the entirety of the structure involved. The Patent and Trademark Office also tried to rely on a morpholino group in the single reference wherein the nitrogen atom has two ethyl groups bonded to it and linked to each other by a single oxygen atom, thereby allegedly providing the "missing" ether oxygen noted above. Again, the Court stated that one could not ignore the entirety of the structure, i.e., the fact that this prior art group compound was cyclic. One could not apply components of structural features of one compound to another in isolation or apart from the group's overall structure. Various other similar allegations made were also rejected by the Court based on similar rationale.

Disclosure of particular generic formulae and/or species with their particular set of structural components, under *Baird* and *Jones*, does not motivate or provide adequate reason to one of ordinary skill in the art to select various structural features from different compounds or from different generic formulae in isolation and apply them to other compounds or other generic formulae.

Nevertheless, even the generic allegation has many shortcomings when applied to this particular case. There is not a single compound containing a biphenyl moiety in the disclosure of Knox. There is also not a single preference disclosed for a compound or group containing a biphenyl moiety. Merely a broad generic formula is provided with one of the substituents being W, which can be optionally substituted aryl among many other groups (see page two, the middle of the second column, where aryl is defined on page 3, about the middle of the second column in paragraph 28, as being one of many groups, including phenyl, which can be substituted with a whole list of groups spanning more than 20 lines, one of which is another substituted phenyl, where the possible substituents of this second phenyl are not even provided.

Nothing in Knox provides any reason to one of ordinary skill in the art to change, e.g., the heteroaryl groups of the compounds 1506-00404 and 1506-08722 of Knox to, e.g., phenyl. Yet, the Office Action appears to treat such as established (which it is not) since the

obviousness rejection starts with allegations assuming that biphenyl groups for substituent W are established or that compounds having biphenyl groups as substituent W are taught by Knox .

The obviousness rejection starts with the allegation that the CF_3 substituent would be prima facie obvious over the unsubstituted examples of Knox in view of Dupuis. As discussed above, no specific example is identified by the Office Action suitable for the alleged modification. No compound of Knox is a CF_3 group apart from a compound of the present claims because for at least not one of them containing a biphenyl moiety.

The Office Action then points to scheme 2 disclosed in Knox on page 12, where halfway through the synthesis an $R1CO_2H$ compound (where R1 is not defined in the scheme) is reacted with an intermediate in the scheme. The Office Action then alleges that Dupuis teaches such a compound $R1CO_2H$, which is a biphenyl compound having a CF3 group and a CO_2H group, and since this compound is allegedly readily available, one of ordinary skill in the art would favourably pick it. No reason other than availability is alleged, which is clearly inadequate under the precedential decisions discussed above.

Moreover, not only are the structures of the compounds of Knox and Dupuis completely different, so are the properties of the compounds thereof, again providing no reason to one of ordinary skill in the art for even considering these two references together. The compound in Dupuis discussed above is identified on page 6525 as Xenalipin, which on page 6524, second column, last paragraph, is taught to be a non-natural product which reduces cholesterol and triglyceride levels in plasma, while the compounds of Knox are taught to be useful for treating VEGF-mediated diseases, e.g., endometriosis, etc. See abstract, for example.

Regarding scheme 2 in Knox, every single compound prepared by said scheme (see disclosure on pages 12-13, examples 1-6, yields a compound completely different from the presently claimed invention, none of which contain a biphenyl group, and none of which have a CF_3 substituent.

It is also unclear from the Office Action which of the presently claimed compounds would be obvious in view of the above-cited references. For example, the elected species of the present claims, i.e., N-methyl-N-(1-methyl-2-oxo-2-phenethyl)-2-[1-(4'-trifluoromethylbiphenyl-2-carbonyl)piperid-4-yl]thiazole-4-carboxamide, which is the ninth compound in claim 15 and is disclosed in the specification on page 46 as compound number 38, is not even within the broadest generic disclosure of Knox. The definition of Q in the generic formulae

in Knox does not contain an H group, which is the group present in the elected species in the corresponding position. See page 2, second column toward the top portion thereof.

Nothing in the cited references teaches or suggests the presently claimed invention.

Reconsideration is respectfully solicited.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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